

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

IN RE: TESTOSTERONE REPLACEMENT THERAPY PRODUCTS LIABILITY LITIGATION	MDL No. 2545
This Document Relates to All Cases	Master Docket Case No. 1:14-cv-01748 Hon. Judge Matthew F. Kennelly

APPENDIX B
(Studies Showing TRTs Improve or Do Not Change Cardiovascular Risk)¹

	Study	Key Finding
1	Molly M. Shores et al., <i>Testosterone Treatment and Mortality in Men with Low Testosterone Levels</i> , 97 J. CLIN. ENDOCRINOL. METAB 2050 (2012)	"[T]estosterone treatment was associated with . . . a 39% decreased mortality risk."
2	Vakkat Muraleedharan et al., <i>Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes</i> , 169 EURO. J. ENDOCRINOL. 725 (2013)	"There was a significant increase in mortality rate (20.11% 35/174)) in the untreated group, in comparison with 9.38% (6/64) in the treated group and 9.12 (31/340) in the normal group." The researchers concluded: "This study demonstrates that long-term testosterone replacement is not only safe in terms of mortality but may also improve survival in men with type 2 diabetes and hypogonadism. . . . These findings are also in line with the beneficial effects of TRT on cardiovascular risk factors in men with low testosterone that include insulin resistance, central obesity and cholesterol lowering and also suggest that these might be translated into long-term survival benefits."
3	Olga M. Calof et al., <i>Adverse Events Associated With Testosterone Replacement in Middle-Aged and Older Men: A Meta-Analysis of Randomized, Placebo-Controlled Trials</i> , 60A J. GERONTOLOGY: MED. SCIENCES 1451 (2005).	"Cardiovascular event rates did not differ significantly between testosterone-treated and placebo-treated men."

¹ Copies of these studies are maintained in Defendants' files, and they will gladly provide them to chambers should the Court like to review any or all of them.

4	M. Fernandez-Balsells et al., <i>Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis</i> , 95 J. CLIN. ENDOCRINOL. METAB. 2560 (2010)	"There were no significant differences in the rates of death, myocardial infarction, revascularization procedures, or cardiac arrhythmias between the testosterone and the placebo [] groups."
5	Jacques Baillargeon et al., <i>Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy</i> , ANNALS PHARMACOTHERAPY 1 (2014)	"In this matched double cohort study of more than 24,000 Medicare beneficiaries, we found that the use of intramuscular testosterone therapy was not associated with an increased risk of MI," and "[f]or patients in the highest quartile [for the MI prognostic group], receipt of testosterone therapy was associated with a decreased risk of MI."
6	Kay-Tee Khaw et al., <i>Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men: European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study</i> , 116 CIRCULATION 2694 (2007)	"In the present study population of men, increasing endogenous testosterone concentrations appeared to be inversely related to mortality due to all causes, cardiovascular causes and cancer, with \approx 25% to 30% lower risk of total mortality in the highest compared with the lowest quartile of testosterone level. A 1-SD [standard deviation] increase in testosterone level was associated with an \approx 14% lower risk of total mortality."
7	Jonathan C. Brooke et al., <i>Cardiovascular safety and testosterone replacement therapy in male hypogonadism including men with type 2 diabetes and cardiovascular disease</i> , ENDO. REV. (3 Meeting Abstracts) MON-42 (2012)	"This audit confirm the cardioprotective role of physiological doses of testosterone and demonstrates that in clinical practice TRT has beneficial effects on cardiovascular risk factors including circulating lipid and cholesterol levels. . . . TRT was not associated with an increase in . . . MACEs [major adverse cardiovascular events] or mortality."
8	Per Marin et al., <i>Androgen Treatment of Abdominally Obese Men</i> , 1 OBESITY RESEARCH 245 (1993)	"Beneficial results only in the group treated with T and not in the groups treated with DHT or placebo. . . . The results indicate an improvement of risk factors for cardiovascular disease"
9	Camilla M. Hoyos et al., <i>Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: a randomised placebo-controlled trial</i> , 167 EURO. J. ENDOCRINOL. 531 (2012)	"We demonstrate that 18 weeks of testosterone therapy . . . improve[s] several important cardiometabolic risk factors"
10	Giovanni Corona et al., <i>Testosterone and Metabolic Syndrome: A Meta-Analysis Study</i> , 8 J. SEX. MED. 272 (2011)	"The analysis of the available [Randomized Clinical Trials] demonstrated, for the first time, that TRT in subjects with MetS [metabolic syndrome] is able to improve central obesity Central obesity (high waist circumference) is a

		better predictor of an increased cardiovascular risk than obesity per se.” ²
11	Svetlana Y. Kalinchenko et al., <i>Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study</i> , 73 CLIN. ENDOCRINOL. 602 (2010)	“In conclusion, in this short study of administration of T to men with the [metabolic syndrome], a number of risk factors for . . . cardiovascular disease showed improvement.”
12	Antonio Aversa et al., <i>Effects of Testosterone Undecanoate on Cardiovascular Risk Factors and Atherosclerosis in Middle-Aged Men with Late-Onset Hypogonadism and Metabolic Syndrome: Results from a 24-month, Randomized, Double-Blind, Placebo-Controlled Study</i> , 7 J. SEX. MED. 3495 (2010)	“The present study shows that in the same patient population, TU [testosterone undecanoate] for 24 months ameliorates both insulin resistance and visceral adiposity which are factors associated with a higher risk of death.”
13	Armin E. Heufelder et al., <i>Fifty-two-Week Treatment with Diet and Exercise Plus Transdermal Testosterone Reverses the Metabolic Syndrome and Improves Glycemic Control in Men with Newly Diagnosed Type 2 Diabetes and Subnormal Plasma Testosterone</i> , 30 J. ANDROLOGY 726 (2009)	“The addition of a relatively low-dose testosterone preparation . . . raising serum testosterone concentrations to the lower range of normal, led to a significant, additional, improvement of glycemic control, insulin sensitivity, and reversal of the MetS [metabolic syndrome] in most participants.”
14	Anne M. Kenny et al., <i>Effects of Transdermal Testosterone on Bone and Muscle in Older Men with Low Bioavailable Testosterone Levels, Low Bone Mass, and Physical Frailty</i> , 58 JAGS 1134 (2010)	“The current study found no differences in cholesterol levels or cardiovascular events between the testosterone and placebo groups.”
15	Atish Mathur et al., <i>Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men</i> , 161 EURO. J. ENDOCRINOL. 443 (2009)	“In this study, we have demonstrated that testosterone therapy significantly delays time- to exercise-induced MI [myocardial ischaemia]. This is consistent with the findings in our previous studies; however, in the present study the clinical effect was maintained and sustained for a longer period of 12 months.”
16	T. Hugh Jones et al., <i>Testosterone Replacement in Hypogonadal Men with Type 2 Diabetes and/or</i>	“The current study showed a trend for cardiovascular events to occur more frequently in the placebo group than in the TRT group.”

² Metabolic syndrome is a set of “risk factors” that places a person at a “higher risk” of cardiovascular disease. AM. HEART ASSOC., *About Metabolic Syndrome*, http://www.heart.org/HEARTORG/Conditions/More/MetabolicSyndrome/About-Metabolic-Syndrome_UCM_301920_Article.jsp

	<i>Metabolic Syndrome (the TIMES2 Study)</i> , 34 DIABETES CARE 828 (2011)	The researchers further found, “This study has shown that TRT in hypogonadal men with type 2 diabetes and/or MetS [metabolic syndrome] improves several cardiovascular risk factors”
17	Chris J. Malkin, <i>Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial</i> , 27 EURO. HEART J. 57 (2006)	“Over the study period testosterone therapy appeared safe, with no excess of serious adverse events.”
18	Carolyn M. Webb et al., <i>Effects of Oral Testosterone Treatment on Myocardial Perfusion and Vascular Function in Men with Low Plasma Testosterone and Coronary Heart Disease</i> , 101 AM. J. CARDIO. 618 (2008)	“Our results provide evidence that oral TU [testosterone undecanoate] has a beneficial effect on arterial stiffness in older men with testosterone at or less than the lower limit of normal range. In light of recent research showing that arterial stiffness was a predictor of cardiovascular outcomes, our results may suggest that in the longer term, oral TU could potentially confer cardiovascular benefit through its effects on arterial stiffness.”
19	Marianna Yaron, <i>Effect of testosterone replacement therapy on arterial stiffness in older hypogonadal men</i> , 160 EURO. J. ENDOCRINOL. 839 (2009)	“These studies [referring to other studies including Webb et al. study referenced above], including our own, collectively lend support to the possibility that testosterone has a favorable effect on large artery stiffness.”
20	Kerry L. Hildreth et al., <i>Effects of Testosterone and Progressive Resistance Exercise in Healthy, Highly Functioning Older Men with Low-Normal Testosterone Levels</i> , 98 J. CLIN. ENDOCRINOL. METAB. 1891 (2013)	“T supplementation was well tolerated and associated with a lower rate of cardiovascular endpoints in this population.”
21	Katherine M. English, <i>Low Dose Transdermal Testosterone Therapy Improves Angina Threshold in Men with Chronic Stable Angina: A Randomized, Double-Blind, Placebo Controlled Study</i> , 102 CIRCULATION 1906 (2000)	“In this study, we have demonstrated that daily administration of small doses of supplemental testosterone to men with chronic stable angina prolongs the time to myocardial ischemia compared with the effect of placebo.”